

Trends in Kaposi's Sarcoma and Non-Hodgkin's Lymphoma Incidence in the United States From 1973 Through 1998

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Background: The incidence of Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) in the general population has markedly increased since the onset of the AIDS epidemic in 1981. However, during the 1990s, the dynamics of the AIDS epidemic changed, as human immunodeficiency virus (HIV) infection rates slowed and effective antiretroviral therapies were introduced. We examined the impact of these changes on the general population incidence of KS and NHL. **Methods:** Age-standardized incidences for KS and NHL from 1973 through 1998 were obtained from nine population-based cancer registries that participate in the Surveillance, Epidemiology and End Results (SEER) program. **Results:** During the mid-1990s, KS incidence declined sharply in all nine registries. Decreases in KS incidence were most evident in San Francisco, where KS rates among white men had risen from 0.5 per 100 000 people per year in 1973 to between 31.1 and 33.3 from 1987 through 1991 and then declined to 2.8 in 1998. With background NHL incidence in the general population being much higher than that for KS, changes in incidence related to the AIDS epidemic were most evident in subgroups at high risk of AIDS. In San Francisco, NHL rates among white men rose from 10.7 in 1973 to a peak of 31.4 in 1995 and then declined to 21.6 in 1998. NHL types that were most highly AIDS-associated declined most steeply, whereas the incidence of NHL types not associated with AIDS was either stable or increasing. **Conclusion:** Changes in KS and NHL incidence since the mid 1990s may reflect declines in the number of individuals with AIDS and improved immune function in such individuals following the introduction of effective antiretroviral therapies in the 1990s. Notably, non-AIDS-associated NHL incidence has continued to increase steadily through 1998. [J Natl Cancer Inst 2002;94:1204-10]

Before the acquired immunodeficiency syndrome (AIDS) epidemic, Kaposi's sarcoma (KS) was rare in the United States (1), occurring mainly in elderly men from Italy and eastern Europe (2,3). Sporadic reports of KS following organ transplantation appeared with increasing frequency as use of severely immunosuppressive drug regimens given as part of organ transplantation became more widespread, pointing to a role for immunodeficiency in the development of KS (4,5). However, with the onset of the AIDS epidemic in the United States in 1981, KS incidence increased sharply (6,7). Notably, the risk of KS among homosexual men with AIDS was much higher than that among other population groups with AIDS. Moreover, the risk of KS among homosexual men with human immunodeficiency virus

(HIV) infection increased with reported number of sexual partners and with sexual contact with individuals with KS (8). Taken together, these observations suggested that, in addition to HIV, there was a second sexually transmissible causative agent for KS. In 1994, this agent was discovered to be a novel herpesvirus, the Kaposi's sarcoma-associated herpesvirus (KSHV) (9).

However, in the late 1980s, well before the discovery of KSHV and even before the advent of effective antiretroviral therapies, KS incidence in homosexual men with AIDS began to decline (10). Several factors may have contributed to this decline. During the 1980s, American homosexual men responded to the AIDS epidemic by reducing the number of unprotected sex acts with new partners (11,12). This change may have restricted not only the dissemination of HIV but also that of KSHV (13). In addition to the important role of KSHV, having HIV-related immunosuppression increases the risk of developing KS thousands-fold (10). However, beginning in 1987, increasingly effective antiretroviral drugs were developed to treat HIV and AIDS. By 1996, treatments included non-nucleoside reverse transcriptase and protease inhibitors that were combined into regimens called highly active antiretroviral therapy (HAART). Effective antiretroviral therapy in individuals with HIV-related immunosuppression often resulted in a substantial improvement in host immunity, resulting in reduced risk of developing KS (14-19).

Because KS was exceedingly rare in the general population before the onset of the AIDS epidemic (1), almost all cases of KS during the AIDS era could be attributed to AIDS (20). However, changes in NHL incidence related to the AIDS epidemic have been more difficult to track. The risk of developing NHL increased several-hundred-fold among individuals with AIDS (10), but even at the height of the AIDS epidemic, only a small proportion of all NHL cases occurred in individuals with AIDS (21). Furthermore, only a few types of NHL have been associated with AIDS, notably central nervous system (CNS) lymphomas, high-grade immunoblastic and Burkitt's lymphomas and, to a lesser extent, intermediate-grade large-cell diffuse lymphomas (10). In contrast, most low- and intermediate-grade lym-

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phomas are not AIDS-associated, including small-cell lymphocytic and follicular lymphomas.

Recent advances in the treatment of individuals with AIDS have reduced the risk of both NHL, especially CNS lymphomas, and KS. These findings come from selected populations in longitudinal studies and from data collected soon after the introduction of HAART but before many individuals with AIDS were yet using it (10,22). Therefore, the results of these studies cannot readily be extended to trends of KS and NHL incidence in the general population of the United States. The incidence of these cancers may be affected by trends in the AIDS epidemic, such as the changing degree to which individuals with AIDS take effective antiretroviral therapy and the emergence of HIV resistance to these therapies (23), by HIV incidence and the proportion of individuals with AIDS who are homosexual men (24,25) and, more speculatively, by changes in sexual behaviors that reduce KSHV transmission. In this article, we describe the incidence of KS and NHL in the general population of the United States, as represented in the Surveillance, Epidemiology and End Results (SEER)¹ program of the National Cancer Institute, between 1973 and 1998.

METHODS

The data for KS and NHL incidence between 1973 and 1998 were obtained from nine population-based cancer registries that have participated in the SEER program since 1973 and include areas with high AIDS incidence, such as the metropolitan areas of San Francisco, Seattle (from 1974), Atlanta (from 1975), and Hawaii; areas with intermediate AIDS incidence, such as Detroit, Connecticut, and New Mexico; and areas of low AIDS incidence, such as Iowa and Utah. In total, these registries encompass about 10% of the United States population (26). All cases coded by the International Classification of Disease—Oncology, 2nd Edition (ICD-O-2) (27) as KS (histology 9140) or as NHL (9590–9595 and 9670–9717) from 1973 through 1998 were included in the analyses, regardless of primary site. Age-standardized incidence rates of KS and NHL were calculated by using the 1970 United States standard population and were expressed as the number of cases per 100,000 people per year. Subset data were analyzed by ethnicity (white and African-American), sex, geographic area, and age (20–54 years and 55 years or older).

To focus on AIDS-associated NHL types, we examined changes in NHL incidence from 1978 through 1998, during which time the detailed ICD-O-2 type codes for NHL types were in use. The observed changes in NHL incidence between 1978 and 1998 were not attributable to temporal variation in the proportion of NHLs being reviewed by pathologists or in their classifications by histologic type (analysis not shown). Lymphomas were grouped by site into peripheral or CNS lymphoma (ICD-O-2 site codes C710–729) and by histology types defined as AIDS-associated (immunoblastic lymphoma [ICD-O-2 histology code 9684]; Burkitt's lymphoma, including small-cell, noncleaved lymphoma [9686 and 9687]; and intermediate-grade large-cell diffuse lymphomas [9680–9683 and 9593]). For comparison, we present data on some lymphoma types not associated with AIDS (small lymphocytic [9670–9671] and follicular and nodular lymphoma [9690–9698]) (28). The sum of these NHL types does not total all NHLs because not all cases of NHL have type information and because not all types were included.

RESULTS

Kaposi's Sarcoma

Between 1973 and 1998, 12,162 cases of KS were diagnosed in the SEER registry areas of surveillance, 88% of them occurring among white men. In the pre-AIDS period (i.e., from 1973 through 1978), 11% of all KS patients were 20–54 years of age, whereas since 1978 more than 90% of KS patients have been in that age group. KS incidence among white men rose steeply in the 1980s from 0.3 in the pre-AIDS period to a broad peak of between 8.1 and 7.8 between 1989 and 1991, respectively (Fig. 1). African-American men had similar KS incidences rates; however, KS incidence peaked about 2 years later than it did in white men, and peak rates were 8.6 and 8.0 in 1992 and 1994, respectively. Between 1995 and 1998, there was a precipitous fall in KS incidence rates, to 0.9 among white men and 2.4 among African-American men. Among African-American women, KS incidence rates rose from 0.07 in 1987 to a peak of 0.49 in 1996 (Fig. 2). By contrast, the KS incidence rate among white women, which was always low (0.07 from 1973 through 1978), changed little (0.09 from 1979 through 1998) over the past 25 years.

KS incidence increased after 1981 in all registries. Geographically, KS incidence among men was highest in San Francisco, Hawaii, Atlanta, and Seattle. Among white men in San Francisco, KS incidence rates averaged 32.1 in a broad peak between 1987 and 1992, whereas in Atlanta, Hawaii, and Seattle, the KS incidence rates averaged 8.4, 8.4, and 4.6, respectively, between 1987 and 1994. However, by 1998, KS incidence rates among white men declined in all of the nine registries. Specifically, declines of more than 90% occurred in San Francisco (to 2.8), Seattle (to 1.0), Hawaii (to 0.7), and Atlanta (to 0.6). In addition, by 1998, low-AIDS-risk areas (Utah and Iowa) had KS incidence rates among white men of 0.8 and 0.11, respectively—that is, only slightly higher than the incidence rates of the pre-AIDS period.

Non-Hodgkin's Lymphoma

NHL incidence in the general population had been steadily increasing for several decades before the onset of the AIDS epidemic in 1981 (Fig. 1). Throughout the 1980s, NHL incidence increased at a faster rate than during the pre-AIDS period. Beginning in the early 1990s, NHL incidence began to stabilize and then to decline, especially among white men. In 1973, the NHL incidence rate among white men was 10.4; by 1983 it had increased to 14.5; and by 1993 it had almost doubled, to 20.1. NHL incidence among white men peaked at 21.1 in 1995 and then declined to 19.0 in 1998. In African-American men, NHL incidence was 8.8 in 1973, rose to 9.7 in 1983, and almost doubled to 15.6 in 1993. NHL incidence in African-American men peaked at 19.7 in 1995 and then declined to 12.9 in 1998.

The incidence of NHL among white men in the San Francisco registry has declined markedly since 1995. After a broad peak in NHL incidence between 27.0 and 31.4 from 1990 through 1996, incidence in white men declined to 21.6 in 1998. With smaller numbers of NHL cases in African-American men than in white men, incidence rates in African-American men were less stable; however, NHL incidence peaked between 22.0 and 23.0 from 1993 through 1997 before falling to 11.6 in 1998 (Fig. 1). Similar but less impressive patterns in NHL incidence were seen

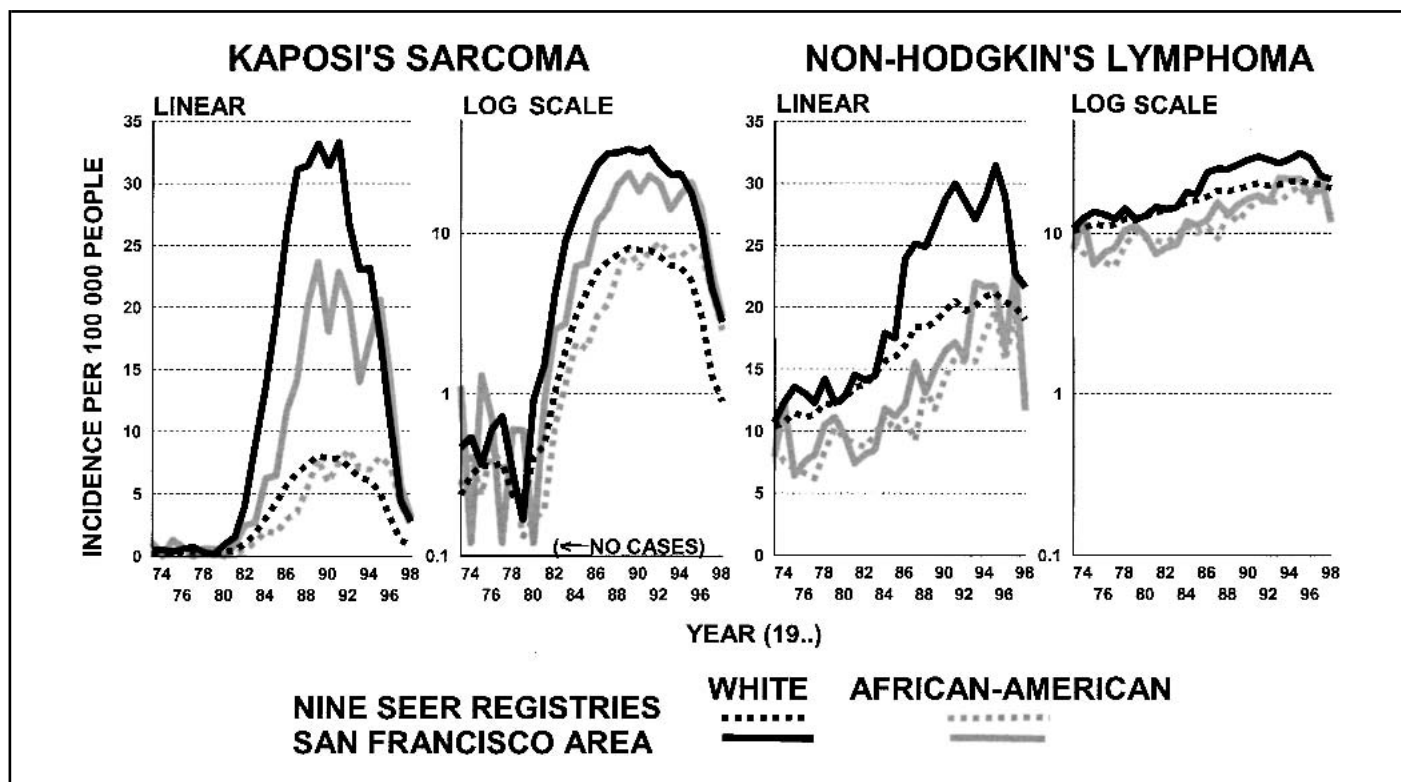


Fig. 1. Kaposi's sarcoma and non-Hodgkin's lymphoma incidence among men, per 100 000 people per year, age-standardized to the 1970 U.S. population, shown on a linear and log scale to illustrate both the absolute and relative changes in nine Surveillance, Epidemiology and End Results (SEER) registries and in the San Francisco area registry only, from 1973 through 1998. Years with no cases were set arbitrarily at 0.12 cases in the log scale.

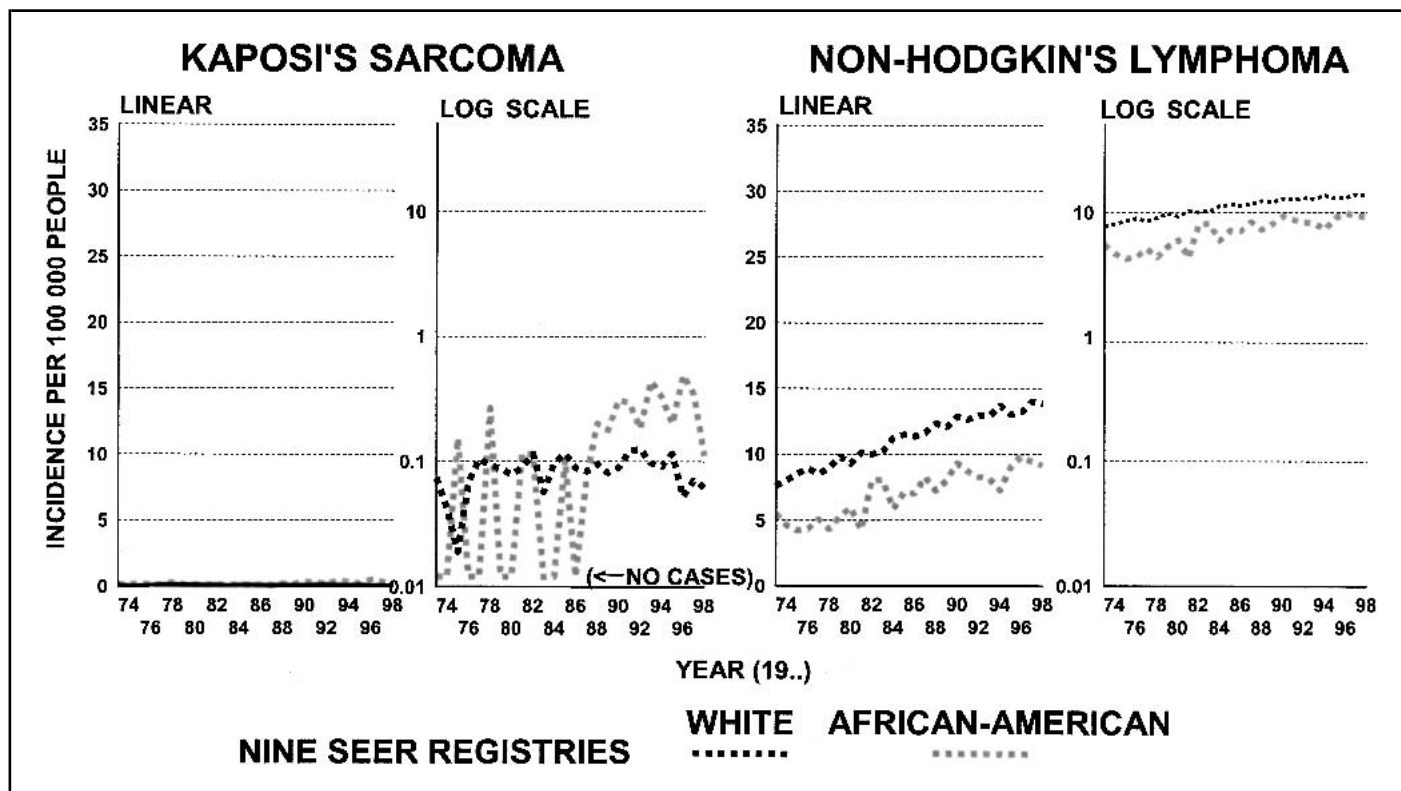


Fig. 2. Kaposi's sarcoma and non-Hodgkin's lymphoma incidence among women, per 100 000 people per year, age-standardized to the 1970 U.S. population, shown on a linear and log scale to illustrate both the absolute and relative changes in nine Surveillance, Epidemiology and End Results (SEER) registries from 1973 through 1998. Incidence patterns for women in the San Francisco area registry are not presented, because AIDS incidence among women in San Francisco was too low to have an impact on cancer incidence. Years with no cases were set arbitrarily at 0.12 cases in the log scale.

among white and African-American men in data from other high-AIDS-incidence areas (data not shown). NHL incidence rates among women were slightly more than one half those in men and were not affected by the onset of the AIDS epidemic (Fig. 2). Among white women, the 1973 NHL incidence rate was 7.6, rising to 10.2 by 1983 and to 12.9 by 1993. The incidence of NHL in white women continued to increase thereafter, reaching 13.8 in 1998. Among African-American women the NHL incidence rate was 5.5 in 1973, 8.1 in 1983, 8.2 in 1993, and 9.1 in 1998.

NHL incidence categorized by disease site and histologic type was used to examine changes in AIDS-associated NHL types in white men (Fig. 3). In all SEER registries, CNS lymphoma incidence in white men rose from 0.02 (based on only two cases) in 1973 to a peak of 1.3 in 1995 and then declined to 0.5 in 1998. Throughout the 1980s and 1990s, CNS lymphoma incidence was higher in the San Francisco registry than in any other SEER registry, but incidence stabilized during the early 1990s. The highest incidence of CNS lymphoma in San Francisco was 3.3 in 1995, but by 1998 incidence had fallen to 1.0. Evaluation of NHL by histologic type revealed that the incidence of immunoblastic lymphoma in San Francisco peaked at 3.8 in 1990 and fell to 0.4 by 1998. Similarly, the incidence of Burkitt's lymphoma peaked at 2.6 in 1989 and then declined to 0.7 in 1998 (Fig. 3). The incidence of another AIDS-associated

NHL type—intermediate-grade large-cell diffuse lymphoma—was higher in white men in the San Francisco registry than in the other SEER registries; incidence declined from a peak of 10.7 in 1995 to 7.9 in 1998.

In contrast, the incidence of NHL types not associated with AIDS increased among white men throughout the 1980s and 1990s. The incidences of follicular and nodular lymphoma, for example, were 2.6, 2.8, and 3.5 in 1978, 1988, and 1998, respectively, in all SEER registries, and 3.3, 3.5, and 3.6 in the San Francisco registry (Fig. 3). The same pattern was observed for small-cell lymphocytic lymphoma (Fig. 3), another NHL type that is not associated with AIDS. Similar but less pronounced changes in the incidence of these NHL types were observed among African-American men (data not shown). In keeping with the low rate of HIV infection among white and African-American women, no statistically significant changes in the incidence of either CNS lymphoma or in AIDS-associated NHL histologic types were seen (data not shown).

DISCUSSION

We have observed remarkable changes in both KS and NHL incidence in the United States population during the past two decades. For both cancers, a rise in their incidence during the 1980s was clearly related to the onset of the AIDS epidemic.

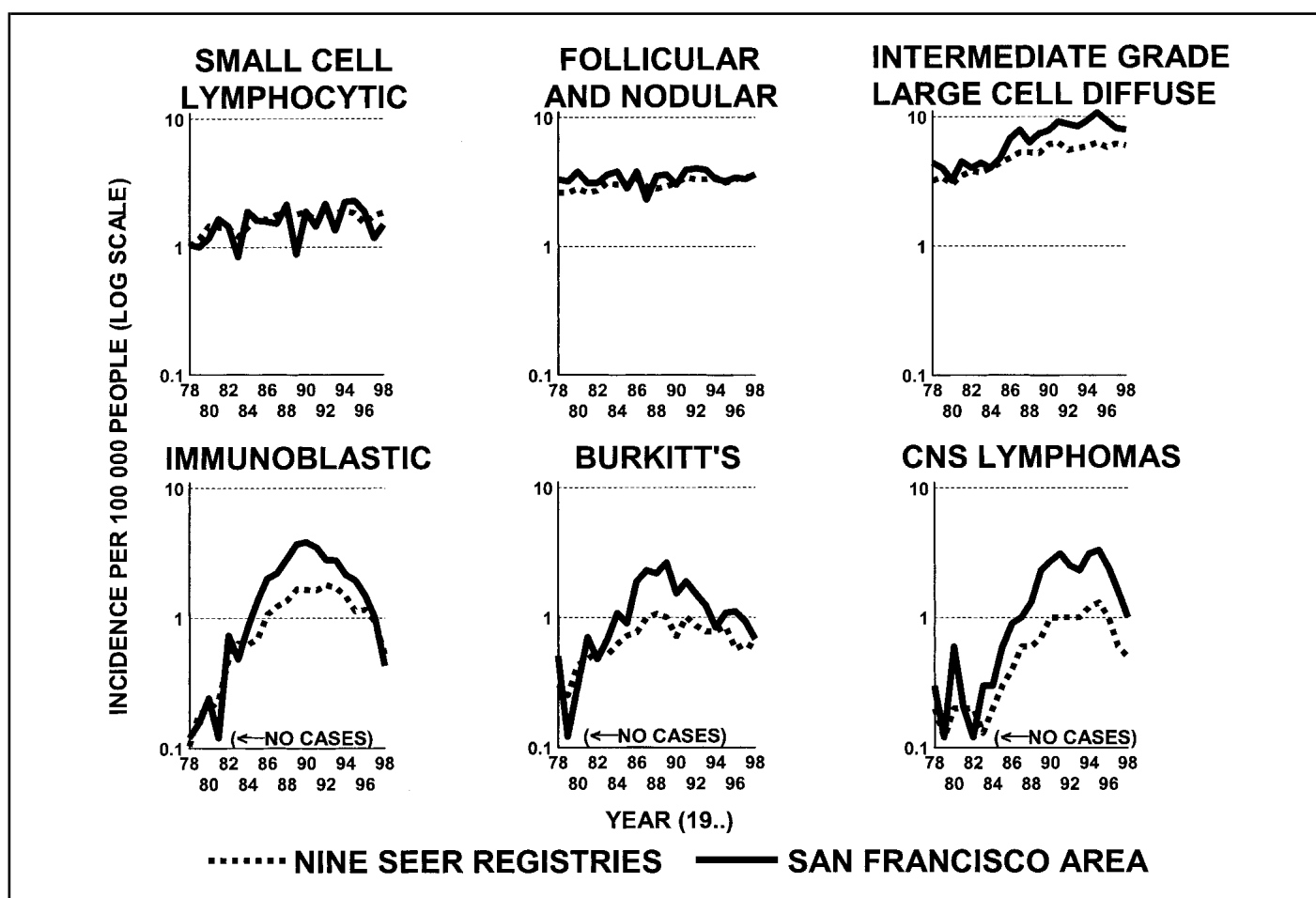


Fig. 3. Selected non-Hodgkin's lymphoma types among white men, per 100 000 people per year, age-standardized to the 1970 U.S. population, shown on a log scale in nine Surveillance, Epidemiology and End Results (SEER) registries and in the San Francisco area registry only, from 1978 through 1998. CNS = central nervous system. Years with no cases were set arbitrarily at 0.12 cases in the log scale.

Similarly, the declines in KS and NHL incidence during the 1990s paralleled changes in the incidence of AIDS in response to changes in both the risk of HIV infection and improved therapies. For KS, the rise in incidence was abrupt and dramatic because KS was very rare prior to the AIDS epidemic. However, the NHL incidence changes were subtle, being superimposed on a much higher background incidence of NHL in individuals without HIV/AIDS. In the general population, NHL incidence increased throughout the 1980s and 1990s, maintaining a pattern of increase that has been ongoing for several decades (29). The additional cases of NHL associated with AIDS further accelerated this increase until the AIDS-associated increases tapered off in the mid 1990s.

The recent KS epidemic has been dominated by high-risk groups, such as homosexual men, who have an increased exposure to both HIV/AIDS and KSHV. Thus, the resulting AIDS-associated KS epidemic during the past two decades occurred disproportionately in geographic areas with relatively large populations of homosexual men, such as San Francisco, Hawaii, Atlanta, and Seattle. By contrast, women experienced a much smaller KS epidemic, reflecting their lower risk of HIV infection and also their lower prevalence of KSHV (30,31). Although KS incidence rates among white and African-American men followed the same general pattern, the KS incidence rate among African-American men rose and then declined slightly later than among white men. A recent study has shown that HIV infection rates in African-American men did not decrease as sharply as they did in white men and that homosexual transmission of HIV continues to contribute to the higher HIV infection rates in African-American men (32). In addition, African-American men, as a group, have less access to health care and are less likely to receive advanced antiretroviral therapies (33). Nevertheless, KS incidence in this group is also now declining.

The KS incidence rates presented in this study are consistent with clinical experience that KS is now an uncommon condition. Even in San Francisco, an epicenter for HIV infection and AIDS in homosexual men, the KS incidence in the general population was only about three cases per 100 000 people in 1998, and it was half that number in most of the other areas that participate in the SEER program. Several factors have probably contributed to the decline in KS incidence. First, the incidence of HIV infection and AIDS declined during the late 1980s and early 1990s in all population groups; however, the decline was most notable among homosexual men (32), the group with the greatest KS risk. Second, when homosexual men modified their sexual behavior to prevent HIV transmission, they also probably reduced their risk of KSHV infection (13,34), thereby lowering their KS risk even further. We note, however, that not all studies agree that KSHV prevalence in the male homosexual population has declined (35). Third, antiretroviral therapies have gradually improved in their efficacy since being introduced during the late 1980s, which has resulted in improved immunity among HIV-infected individuals thereby lowering the risk of KS, even among those who are co-infected with KSHV. It is noteworthy that the incidence of KS began to stabilize in the late 1980s and declined by 1994, well before 1996, when HAART therapies became widely used (36). Our data are consistent with the notion that antiretroviral therapies used in the early 1990s, and perhaps even single-drug regimens used in the late 1980s, reduced the risk of KS. HAART therapy of HIV-infected individuals is likely to have further contributed to the decline in KS incidence

between 1996 and 1998. However, we cannot separate the precise contribution of HAART to the decreased KS risk from the contributions of decreases in the incidences of HIV/AIDS and KSHV infection or the use of other non-HAART therapies.

Changes in KS incidence over the past two decades are dramatic, whereas changes in NHL incidence are obscured by the high background incidence of NHL in the general population. Overall NHL incidence in the United States and elsewhere has been steadily increasing for decades (29). In our study, these increases were observed for white men and women between 1973 and 1979, before the rise of NHL cases associated with the AIDS epidemic increased overall NHL incidence. Throughout this period, NHL incidence in African-American men and women was lower than in white men and women and, having fewer NHL cases, the incidence rates were less stable. However, rates showed similar overall patterns.

The recent decline in AIDS incidence has led to an apparent stabilization or even lowering of overall NHL incidence, especially in men. This stabilization is misleading with respect to NHL changes in the overall population. Our data indicate that the incidence of NHL types not considered AIDS-associated and of NHL in groups at low risk of AIDS, such as men aged 55 years and older and women of all ages, has continued to increase throughout the 1980s and 1990s. The apparent stabilization of NHL incidence in white men during the 1990s appears to reflect the declining NHL incidence in individuals with AIDS.

In earlier analyses, the incidence of specific NHL histologic types was reported to be changing during the 1980s, with some types rising and others falling (28). Our results emphasize that the stabilization in overall NHL incidence from the mid 1990s was related to marked declines in AIDS-associated NHL types. This finding was most prominent in data from SEER registries in high-AIDS-risk areas, such as San Francisco, and in NHL analyses of sites (e.g., CNS) and histologic types (e.g., immunoblastic and Burkitt's lymphoma) that are AIDS-associated. The incidence of intermediate-grade large-cell diffuse lymphoma also declined during the same period, although not as markedly as that of other NHL types associated with AIDS. Although the incidence of large-cell diffuse lymphoma is clearly increased in individuals with AIDS, a large proportion of patients with this lymphoma type do not have AIDS, thus obscuring the impact of the AIDS epidemic on the incidence of this tumor.

As with KS, the decline in AIDS-associated NHL incidence may also be due to decreasing HIV/AIDS incidence and improving therapies for those with HIV infection and its associated immunosuppression. Unlike the situation with KS, where we speculate that a decreased incidence of KSHV may also have contributed to the decline in KS incidence, there is no evidence of a decline in the prevalence of Epstein-Barr virus, a viral cofactor implicated primarily in the development of primary brain lymphomas (37,38) and also in some peripheral-site NHLs in individuals with AIDS (39).

Like other registry-based studies, our study has several potential limitations. First, the most recent SEER registry data, although adequate for cancer surveillance, are likely to become more complete with late reports of additional cancer cases (40), thus slightly increasing the incidence rates of KS and NHL. Second, the incidence of KS and NHL that we report may not be directly applicable to the entire U.S. population, because AIDS incidence varies by community and may be different in SEER registry areas than in other geographic locations. Other limita-

tions of this study include the lack of individual data on AIDS-exposing behaviors, on immune status, and on antiretroviral therapies. In addition, the extent to which cancers in individuals with AIDS are under-reported to cancer registries is unknown, although such under-reporting is unlikely to have affected the downward incidence of AIDS-associated cancers only in recent years.

To summarize, we observed that the incidence of both KS and NHL among men in the nine SEER registries whose data we analyzed increased greatly in the 1980s to broad peaks in the early 1990s and then declined dramatically between 1996 and 1998. Similar results suggesting that the incidences of KS and AIDS-associated NHL types were decreasing by 1996 were also recently reported from Australia (41). We attribute these recent changes in incidence mainly to a decline in the number of individuals with HIV/AIDS-related immunosuppression, which is a consequence of both a decline in HIV/AIDS incidence and the introduction of increasingly effective antiretroviral therapies, including HAART, throughout the 1990s. With these therapies becoming more widely used, HIV-infected individuals are living longer, albeit with only partially reconstituted immune systems, which raises the specter of increasing KS and NHL incidence in the future. As of 1998, there was no indication of a rebounding KS or NHL incidence in the general population. However, if antiretroviral therapies fail to maintain immune competency because of the emergence of HIV resistance, then these favorable trends in KS and NHL incidence could reverse.

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NOTES

¹*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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